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Ruthenium-catalyzed aerobic oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes: a new route to isoquinolones†

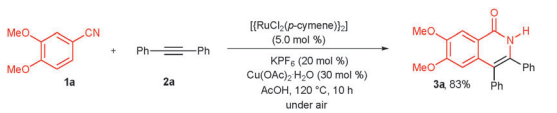
Mallu Chenna Reddy, Rajendran Manikandan and Masilamani Jeganmohan*

The oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes in the presence of a catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$], $Cu(OAc)_2{\cdot}H_2O$ and KPF_6 in acetic acid under air gave isoquinolones in good to excellent yields.

Substituted isoquinolones are one of the important classes of heterocyclic compounds. This core is present in various natural products and biologically active molecules.[1] Due to their interesting biological properties, the development of a highly efficient and easily accessible method to synthesise isoquinolone derivatives is highly important in organic synthesis. Several methods to synthesise isoquinolone derivatives are available in the literature.[2] Among them, metal-catalyzed oxidative cyclization of heteroatom substituted aromatics with alkynes *via* chelation-assisted C–H bond activation is one of the promising and practical methods.[3] Rhodium and ruthenium complexes have been widely used as catalysts for this type of cyclization reaction. Oxidative cyclization of *N*-alkyl or aryl substituted benzamides (Ph-CONHR) with alkynes in the presence of rhodium- or ruthenium catalysts and a stoichiometric amount of external oxidants gave *N*-alkyl or aryl substituted isoquinolone derivatives.[4] In the meantime, *N*-alkoxy benzamides (Ph-CONHOR) reacted with alkynes in the presence of rhodium- or ruthenium catalysts to provide isoquinolone derivatives.[5] In the reaction, the *N*-alkoxy moiety acted as an internal oxidant. But, in the cyclization of benzamides (Ph-$CONH_2$) with alkynes, only 1 : 2 oxidative cyclization products (one benzamide and two alkynes) were observed, and the expected isoquinolone derivatives were not observed.[4a,6] In order to attain the isoquinolone derivatives selectively and to avoid the competitive 1 : 2 cyclization product, *N*-alkyl or aryl or alkoxy substituted benzamides were used.

In the chelation-assisted metal-catalyzed cyclization reactions, ketone, COOH, amide, imine and oxime substituted aromatics have been used for the cyclization with alkynes. To date, there is no report discussing the cyclization of aromatic nitriles with alkynes. Herein, we report for the first time an unprecedented aerobic oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes in the presence of a catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$], KPF_6 and $Cu(OAc)_2{\cdot}H_2O$ to give isoquinolone derivatives in good to excellent yields.[7] Interestingly, the present catalytic reaction was conducted under an air atmosphere.

When 3,4-dimethoxybenzonitrile (**1a**) was treated with diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol%), KPF_6 (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (30 mol%) in acetic acid at 120 °C for 10 h under an air atmosphere, isoquinolone derivative **3a** was observed in an isolated yield of 83% (eqn (1)) (for detailed optimization studies see ESI†). The cyclization reaction was completely regioselective, in which a less hindered C–H bond of **1a** was involved in the cyclization reaction with **2a.** It is important to point out that to date only substituted benzamides have been used as key reactants to synthesize isoquinolone derivatives in the presence of a metal catalyst *via* C–H bond activation. In the present work, an aromatic nitrile is used as a key reactant to synthesize isoquinolone derivatives.



(1)

The present cyclization reaction was tested with various substituted aromatic nitriles and heteroaromatic nitriles (Table 1). Reaction of electron-donating groups such as OH, OMe, Me and NMe_2 at the *para* position of the aromatic nitriles **1b–e** with **2a** gave isoquinolone derivatives **3b–e** in 76%, 78%, 72% and 82% yields, respectively (entries 1–4). A highly sensitive free OH substituent on the aromatic ring of **1b** was not affected in the reaction (entry 1). Similarly, highly sensitive halogen groups such as I, Br, Cl and F at the *para* position of the aromatic nitriles **1f–i** also efficiently participated in the reaction, affording isoquinolone derivatives **3f–i** in 72%, 70%, 68% and 65% yields, respectively (entries 5–8). The catalytic reaction was tested with 4-cyanophenylboronic acid (**1j**). In the reaction, the corresponding cyclization product **3j** was observed in 72% yield (entry 9). But, the boronic acid moiety was cleaved under the reaction conditions. In the meantime, benzonitrile (**1k**) reacted with **2a** yielding product **3j** in 76% yield (entry 10). Very interestingly, electron-withdrawing groups

Department of Chemistry, Indian Institute of Science Education and Research, Pune 411021, India. E-mail: mjeganmohan@iiserpune.ac.in

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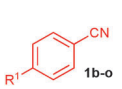
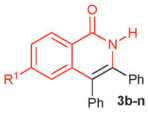
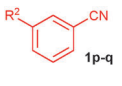
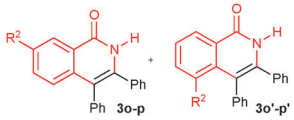
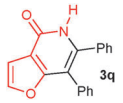
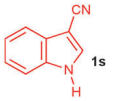
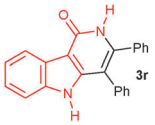
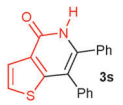
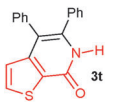
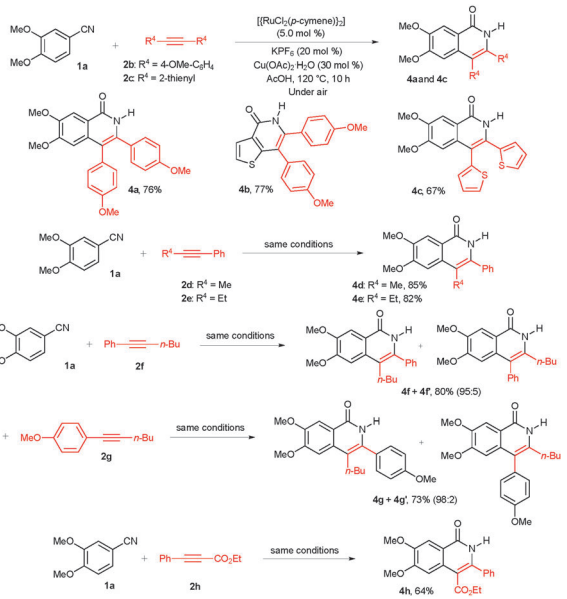
Table 1 The reaction of substituted nitriles **1** with diphenylacetylene (**2a**)[a]

Entry	Nitriles **1b–u**	Products **3b–t**	Yield[b] (%)
			
1	**1b**: R^1 = OH	**3b**: R^1 = OH	76
2	**1c**: R^1 = OMe	**3c**: R^1 = OMe	78
3	**1d**: R^1 = Me	**3d**: R^1 = Me	72
4	**1e**: R^1 = NMe_2	**3e**: R^1 = NMe_2	82
5	**1f**: R^1 = I	**3f**: R^1 = I	72
6	**1g**: R^1 = Br	**3g**: R^1 = Br	70
7	**1h**: R^1 = Cl	**3h**: R^1 = Cl	68
8	**1i**: R^1 = F	**3i**: R^1 = F	65
9	**1j**: R^1 = $B(OH)_2$	**3j**: R^1 = H	72
10	**1k**: R^1 = H	**3j**: R^1 = H	76
11	**1l**: R^1 = CHO	**3k**: R^1 = CHO	73
12	**1m**: R^1 = COMe	**3l**: R^1 = COMe	75
13	**1n**: R^1 = CO_2Me	**3m**: R^1 = CO_2Me	63
14	**1o**: R^1 = NO_2	**3n**: R^1 = NO_2	74
			
15	**1p**: R^2 = OMe	**3o** + **3o′**: R^2 = OMe	41 + 30
16	**1q**: R^2 = Cl	**3p** + **3p′**: R^2 = Cl	25 + 40
17			93
18			86
19			88
20			74

[a] All reactions were carried out using **1a–u** (1.0 mmol), diphenylacetylene (**2a**) (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol%), KPF_6 (20 mol%) and $Cu(OAc)_2 \cdot H_2O$ (30 mol%) in acetic acid (3.0 mL) at 120 °C for 10 h under an air atmosphere. [b] Isolated yield.

such as CHO, COMe, CO_2Me and NO_2 at the *para* position of the aromatic nitriles **1l–o** provided the corresponding isoquinolone derivatives **3k–n** in 73%, 75%, 63% and 74% yields, respectively (entries 11–14). It is important to mention that C–H bond activation of aromatics substituted with electron-withdrawing groups is quite difficult. Interestingly, in the present reaction, the C–H bond of aromatics substituted with electron-withdrawing groups was activated efficiently. Next, the catalytic reaction was tested with *meta* substituted aromatic nitriles such as 3-methoxy **1p** and 3-chlorobenzonitrile **1q** with **2a**. However, the catalytic reaction was not completely regioselective and a mixture of regioisomeric products **3o–3o′** in 41% and 30% and **3p–3p′** in 25% and 40% yields, respectively, was observed (entries 15 and 16). To demonstrate the scope of the cyclization reaction, various heteroaromatic nitriles **1r–u** were examined (entries 17–20). Thus, the treatment of 3-cyanofuran (**1r**) with diphenylacetylene (**2a**) yielded the corresponding cyclization product **3q** in an excellent yield of



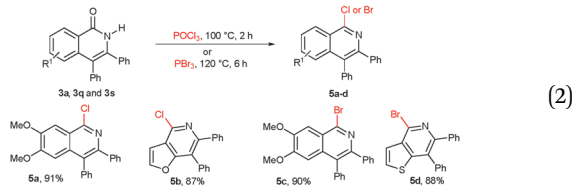
Scheme 1 Regioselective studies of substituted alkynes.

93% (entry 17). Similarly, 3-cyanoindole (**1s**) and 3-cyanothiophene (**1t**) yielded the corresponding cyclization products **3r** and **3s** in 86% and 88% yields, respectively (entries 18 and 19). Interestingly, a less reactive 2-cyanothiophene (**1u**) also efficiently reacted with **2a**, giving cylization product **3t** in 74% yield (entry 20). In substrate **1u**, the electron rich C3–H bond was activated efficiently. (For the reaction of *ortho* substituted benzonitriles with alkynes see ESI†).

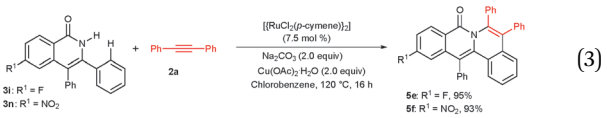
The scope of the catalytic reaction was further tested with various symmetrical and unsymmetrical alkynes (Scheme 1). Thus, symmetrical alkynes such as 1,2-bis(4-methoxyphenyl)ethyne (**2b**) and 1,2-di(thiophen-2-yl)ethyne (**2c**) reacted efficiently with **1a** or **1t** to afford the corresponding cyclization products **4a–c** in 76%, 77% and 67% yields, respectively (Scheme 1). Unsymmetrical alkynes such as 1-phenyl-1-propyne (**2d**) and 1-phenyl-1-butyne (**2e**) cyclized efficiently with 3,4-dimethoxybenzonitrile (**1a**), giving cyclization products **4d** and **4e** in 85% and 82% yields, respectively. The catalytic reaction is completely regioselective, in which the less hindered C–H bond of **1a** was connected to the alkyl (Me and Et) substituted carbon of alkynes **2d** and **2e**. However, 1-phenyl-1-hexyne (**2f**) reacted with **1a**, providing a mixture of regioisomeric products **4f** and **4f′** in a combined yield of 80% with a 95 : 5 ratio of regioisomers. Whereas, methoxy substituted alkyne **2g** afforded regioisomeric products **4g** and **4g′** in a combined yield of 73% (98 : 2 ratio). It is nice to know that the OMe substituent on the phenyl group of the alkyne **2a** increases the selectivity of the reaction. Further, the catalytic reaction was tested with ethyl 3-phenylpropiolate (**2h**) under the optimized reaction conditions. In the reaction, the corresponding cyclization product **4h** was observed in 64% yield in a highly regioselective manner, in which the less hindered C–H bond of **1a** was connected to the ester substituted carbon of alkyne **2h**.

The isoquinolone derivatives were further converted into highly useful 1-chloro and 1-bromo isoquinoline derivatives (eqn (2)). Thus, the reaction of **3a** and **3q** with $POCl_3$ at 100 °C for 2 h gave 1-chloroisoquinoline derivatives **5a** and **5b** in 91% and 87% yields, respectively. Similarly, **3a** and **3s** reacted with PBr_3 at 120 °C for 6 h to yield 1-bromoisoquinoline derivatives **5c** and **5d** in 90%

and 88% yields, respectively (eqn (2)). Further, isoquinolone derivatives **3i** and **3n** reacted with diphenylacetylene (**2a**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$, Na_2CO_3 and $Cu(OAc)_2{\cdot}H_2O$ in chlorobenzene (2.0 mL) at 120 °C for 16 h to yield tricyclic compounds **5e** and **5f** in 95% and 93% yields, respectively (eqn (3)).[4f] In the reaction, the *ortho* C–H bond of one of the phenyl groups and the amide N–H bond of **3i** or **3n** were involved in the cyclization reaction.

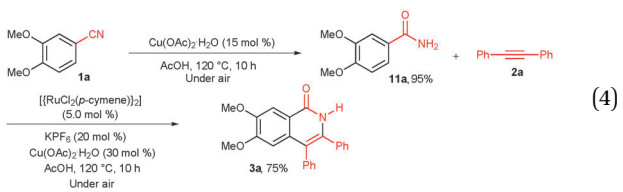


(2)



(3)

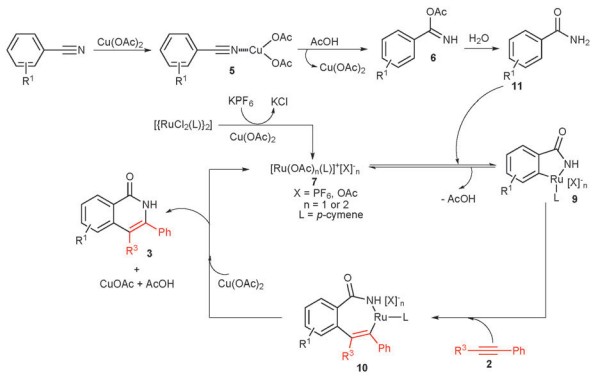
A cooperatively ruthenium- and copper-catalyzed reaction mechanism is proposed for the present cyclization reaction as shown in Scheme 2. In the copper-catalyzed reaction, $Cu(OAc)_2$ likely acts as a Lewis acid to which the CN group of benzonitrile **1** is coordinated to give intermediate **5**. In this stage, $Cu(OAc)_2$ likely reduces the electron density of the nitrile group. Subsequently, nucleophilic addition of AcOH to the CN group in intermediate **5** followed by hydrolysis affords benzamide **11** and regenerates $Cu(OAc)_2$.[8] In the ruthenium-catalyzed reaction, KPF_6 likely removes the chloride ligand from the $[\{RuCl_2(p\text{-cymene})\}_2]$ complex followed by the ligand exchange with $Cu(OAc)_2$, giving cationic ruthenium species **7**. Coordination of the nitrogen group of **11** to the ruthenium cationic species **7** followed by *ortho*-metalation in the presence of AcOH affords a five-membered ruthenacycle **9**.[9] Coordinative insertion of alkyne **2** into the Ru–carbon bond of ruthenacycle **9** provides intermediate **10**. Reductive elimination of intermediate **10** in the presence of $Cu(OAc)_2$ gives product **3** and regenerates the active ruthenium species **7** for the next catalytic cycle. In the reaction, only 30 mol% of $Cu(OAc)_2$ is used as an internal oxidant. The remaining amount of $Cu(OAc)_2$ source is regenerated under oxygen or air from the reduced copper source in the presence of AcOH.



(4)

The proposed mechanism was strongly supported by the following mechanistic evidence (eqn (4)). Treatment of **1a** (1.0 mmol) with AcOH in the presence of $Cu(OAc)_2{\cdot}H_2O$ (15 mol%) at 120 °C in air gave 3,4-dimethoxy benzamide **11a** in 95% yield. Further, the treatment of **11a** with **2a** (1.0 equiv.) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol%), KPF_6 (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (30 mol%) in acetic acid at 120 °C for 10 h in air provided isoquinolone **3a** in an isolated yield of 75%.

In conclusion, we have demonstrated the oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes in the presence of ruthenium and copper catalysts. Further extension of cyclization of substituted nitriles with other π-components and detailed mechanistic investigation are in progress.



Scheme 2 Proposed mechanism.

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